PATENT
Client-Matter No.: 66765-069 (P-UW 3570)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Osborne and Ramesh	Group Art Unit: 1644
Serial No.: 09/323,738	Examiner: G. Ewoldt
Filed: June 1, 1999	Conf. No.: 9582
For: COMPOSITIONS AND METHODS FOR TREATING DIABETES	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Sir:

I, Robert E. Ferrell, declare as follows:

1) I am currently a Professor and the Chairman of the Department of Human Genetics at the Graduate School of Public Health at the University of Pittsburgh. I also hold concurrent positions at the University of Pittsburgh as a Professor in the Department of Pharmaceutical Sciences and as an Affiliate Faculty Member in the Center for Computational Biology and Bioinformatics. I am also an Adjunct Professor of Anthropology at Pennsylvania State University. From 1984 to 1989 I was Professor and Director of the Human Genetics Division in the Department of Biostatistics at the Graduate School of Public Health of the University. Previously, I have held Assistant and Associate Professorships at the University of Texas Health Science Center.

2) I obtained a Bachelors of Science in Chemistry 1966 from Mississippi College and a Ph.D. in Biochemistry from the University of Texas in 1970. I have authored or co-authored numerous papers in the areas of human genetics and biochemistry. My curriculum vitae and list of publications is attached hereto as Exhibit 1.

3) I have reviewed the above-identified patent application. Specifically, I understand that the application describes and claims methods for treating diabetes or forestalling a clinical symptom of diabetes by implanting into a patient cells coexpressing an insulin precursor and a glucose-regulated protease. The insulin precursor contains a proinsulin cleavage site that when cleaved by the glucose-regulated protease results in the generation of mature insulin.

4) I have read the Office Action mailed June 3, 2002, issued in connection with the above-identified application. I understand that the claims have been rejected, in part, because it is alleged that the application does not describe proteases other than furin that are capable of cleaving an insulin precursor sufficient to allow those skilled in the art to practice the invention as claimed.

5) My understanding from reading the application is that there is more than ample description and guidance that directs one skilled in the art to practice the claimed invention with numerous proteases other than furin and with protease cleavage sites recognized by other proteases well known in the art.

6) For example, the application describes specific proteases that can be used to cleave an insulin precursor to produce mature insulin. These proteases are described on, for example, page 18, lines 1-13, and page 37, line 23 through page 38, line 10, and include those that cleave one or more sites in naturally occurring proinsulin as well as other proteases that cleave recognition sites not found in naturally occurring proinsulin.

7) The application also describes, for example, on pages 15-16, that an active insulin molecule of the invention has the function of promoting glucose uptake and consists of an insulin A- and B-chain such as that exemplified by known insulin molecules derived from human or other species.

8) The application further describes on, for example, page 16, line 9 through page 17, line 12, that a proinsulin molecule of the invention simply refers to any precursor form of insulin so long as it contains the A- and B- chains of insulin, or functional fragments thereof. The precursor regions can be either the naturally occurring C-chain or any other sequence such as a linker. Therefore, the application makes known to one skilled in the art that an insulin precursor molecule of the invention can consist of molecules other than those having the naturally occurring configuration of A-, C- and B-chains of a wild type insulin propeptide molecule.

9) The application additionally describes that one skilled in the art can produce an insulin precursor of the invention having a configuration other than the naturally occurring A-, C- and B-chain orientation by engineering insulin A- and B-chains into a single molecule and incorporating protease cleavage sites that allow release of insulin A- and B-chains when cleaved. The configuration can include direct linkage of the A- and B-chains, separated only by the cleavage site, or it can include a spacer region analogous to the naturally occurring C-chain (see, for example, page 16, line 9 through page 17, line 12; pages 26-27, and page 28, line 13 through page 29, line 5). Therefore, the application makes known that the features of an insulin precursor molecule required to practice the invention consist of insulin A- and B-chains and a mechanism, such as one or more protease cleavage sites, that allows separation of the precursor molecule into mature A- and B-chains.

10) Further, the application describes that various protease cleavage sites can be incorporated into an insulin precursor molecule of the invention so long as it has a cognate protease that recognizes and severs the cleavage site. Cleavage sites, and their corresponding proteases, are described, for example, on page 17, line 13 through page 18, line 13; page 29, line 16 through page 30, line 18, and page 37, line 5 through page 38, line 10, and include those selective for naturally occurring insulin as well as those that are completely unrelated to insulin. In this regard, the application describes and exemplifies that a proinsulin cleavage site is engineered to be recognized by either an endogenous or exogenous protease and can

be any sequence that is recognized and specifically cleaved by a protease.

11) Further, at the time the application was filed, it was well known in the art that protease cleavage sites could be incorporated into a polypeptide to effect its cleavage when contacted with the corresponding protease. Several examples of proteases and their corresponding recognition sequences known prior to June 1998, are provided in attached Exhibit 2.

12) Based on the above descriptions, it is clear that an insulin precursor described in the application is not limited to naturally occurring proinsulin containing the naturally occurring protease cleavage sites at the A-chain-C-chain and the C-chain-B-chain junctures. Because an insulin precursor of the invention can contain protease cleavage sites other than those occurring in the naturally proinsulin molecule, the claimed methods are similarly not limited to proteases that recognize and cleave only the sites occurring in the naturally occurring proinsulin molecule. Instead, I understand that an insulin precursor of the invention can constitute essentially any configuration of insulin A- and B-chains incorporating any specifically recognized protease cleavage site that when coexpressed with the cognate protease effects the severing of the insulin A- and B-chains into mature forms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: 15 May, 2003 By: Robert E. Ferrell
Robert E. Ferrell, Ph.D.

January 2003

Curriculum Vitae

NAME: Robert E. Ferrell

DATE OF BIRTH: July 15, 1943

PLACE OF BIRTH: Meridian, Mississippi, USA

ADDRESS: Residence
206 Maple Avenue
Pittsburgh, Pennsylvania 15218
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Graduate School of Public Health
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PROFESSIONAL APPOINTMENTS

2001	Interim Chair, Department of Human Genetics
1994-1995	Chair, Department of Human Genetics
1989-	Professor Department of Human Genetics Graduate School of Public Health University of Pittsburgh
2002-	Affiliate Faculty Member Center for Computational Biology and Bioinformatics University of Pittsburgh
2001-	Associate Member, Center for Pharmacogenetics University of Pittsburgh
2001-	Professor (Secondary Appointment) Department of Pharmaceutical Sciences School of Pharmacy University of Pittsburgh
1984-1989	Professor and Director Human Genetics Division Department of Biostatistics Graduate School of Public Health University of Pittsburgh

1986-	Adjunct Professor of Anthropology Department of Anthropology Pennsylvania State University State College, PA
1987-	Member, Pittsburgh Cancer Institute University of Pittsburgh
1975-1979 1979-1984	Assistant Professor of Population Genetics Associate Professor of Population Genetics Center for Demographic and Population Genetics Graduate School of Biomedical Sciences University of Texas Health Science Center Houston, Texas
1975-1984	Assistant Professor (Adjunct) School of Public Health University of Texas Health Science Center Houston, Texas
1972-1975	Research Associate Department of Human Genetics University of Michigan Medical School Ann Arbor, Michigan

EDUCATION AND TRAINING

1970-1972	U.S. Public Health Service Trainee Department of Human Genetics University of Michigan Medical School
1967-1970	Research Assistant Clayton Foundation Biochemical Institute University of Texas at Austin Ph.D. (Biochemistry) Awarded -- 1970
1961-1966	Mississippi College Clinton, Mississippi B.S. (Chemistry) Awarded -- 1966

ACADEMIC HONORS AND AWARDS

2000	Barbara Bowman Award, Texas Genetics Society
1998	Invention of the Year, Life Sciences Category, University of Maryland (with James Hagberg, Ph.D.)

1998	Chancellor's Distinguished Research Award, University of Pittsburgh
1987	Visiting Professor Department of Medical Genetics Western Pennsylvania Hospital Pittsburgh, PA
1986	Elected to Delta Omega National Public Health Honor Society
1982	Faculty Member Texas Bar Association Family Law Course
1981-1982	President Texas Genetics Society
1973	Elected to Sigma Xi
1970-1972	U.S. Public Health Service Traineeship Department of Human Genetics University of Michigan
1967-1970	Research Assistantship Clayton Foundation Biochemical Institute University of Texas
1965-1966	Undergraduate Honors Research Scholarship Mississippi College

PROFESSIONAL SOCIETIES

American Association for the Advancement of Science

American Society for Human Genetics

American Association of Physical Anthropologists

American Diabetes Association

International Association of Human Biologists

Human Biology Council, Fellow

ADMINISTRATIVE ACTIVITIES

Interim Chair, Department of Human Genetics, University of Pittsburgh, 2001-

Assistant Chair, Department of Human Genetics, University of Pittsburgh, 1998-2001

Chair, Department of Human Genetics, University of Pittsburgh, 1994-1995

Director, Division of Human Genetics, Department of Biostatistics, Graduate School of Public Health, 1984-1989

EDUCATIONAL ACTIVITIES

Teaching

Laboratory Techniques in Biochemistry, Department of Chemistry, University of Texas at Austin, 1968-1969.

Human Genetics 841, Introductory Human Genetics, Team taught, Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, 1971-1973.

Human Genetics, II, Introduction to Human Biochemical Genetics, Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston, Texas, annually, 1977-1984.

Current Topics in Biochemical Genetics, Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston, Texas, 1978-1984.

HuGen 2034. Human Biochemical and Molecular Genetics, Department of Human Genetics, GSPH, 1989-.

Bios 224. Advanced Topics in Human Genetics, Lectures: Genetics of NIDDM and Genetics of Cancer, GSPH, 1984-1990.

Epid 2150. Epidemiology of Cardiovascular Diseases, Lecture: "Genetics of Cardiovascular Disease.", Department of Epidemiology, GSPH, 1984-1986, 1995.

IDM 2011. Health, Disease and the Environment. Module A: Genetic Susceptibility to Disease. Five lecture series, 1986-1992.

Medical Genetics, University of Pittsburgh Medical School, Lectures: "Genetic Susceptibility to Disease." 1985-1992.

Epid 2600. Introduction to Molecular Epidemiology, Lectures: Molecular Genetics of Coronary Artery Disease; Molecular Genetics of Cancer, 1987-1993.

EPIDEM 2900. Epidemiology of Aging, Lecture: Genetics of Aging 1999-

EPIDEM 2601/HUGEN 2601. Molecular Epidemiology Laboratory, Co-teach with Dr. J.S. Dorman, 2001-

Student Supervision

MASTER OF SCIENCE

Graduate School of Biomedical Sciences, University of Texas:

Dunn, Betty S. (1984)
Friedrich, Christopher A. (1984)

Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh:

Marino, Thomas R., Jr. (1985)
"A Genetic Linkage Study of Familial Breast/Ovarian Cancer."

Lyons, Leslie A. (1987)
"Linkage Analysis of Gardner Syndrome and Congenital Hypertrophy of the Retinal Pigment Epithelium."

Cole, Shelley A. (1987)
"Apolipoprotein AI DNA Polymorphisms in the Dogrib Indians."

Iyengar, Sudha (1987)
"Admixture and Association in a Population with Late Onset Diabetes Mellitus: The San Luis Valley Diabetes Study."

Kronz, Lisa M. (1988)
"Possible Linkage Between Autosomal Dominant Aniridia and the Acid Phosphatase-1 Locus on Chromosome Arm 2p."

Hauselman, Ellyn D. (1989)
"Gene Centromere Mapping in Human Ovarian Teratomas: Chromosome 1p."

Chen, Xiao-Qing (1989)
"RFLPs in the Insulin Receptor Gene and Type II Diabetes in Mexican Americans."

Oleck, Joanne R. (1990)
"Genetic Mapping In Breast Cancer Families by Linkage Analysis."

Coe, Sandra J. (1991)
"Family Study of Intracranial Berry Aneurysms."

Deyo, Adrienne M. (1993)
"Isolation and Characterization of a Series of Highly Informative CA Repeat Markers on Chromosome 13"

Perry, Yvette (1993)
"Polymorphism Within the LCAT Region of Chromosome 16"

Hong, H.K. (1993)
"Genetics and Biology of Human Ovarian Teratomas: Recombination Analysis of Chromosome 13q in Ovarian Teratomas"

Jackson, Kelly E. (1994)
"An Exon-2 Peripherin/RDS Mutation Causes Macular and Peripheral Retinal Degeneration"

Johnson, Kimberly (1995)
"X-Linked Exudative Vitreoretinopathy Caused by an Arginine to Leucine Substitutions in Exon 3 of the Norrie Disease Gene"

Easton, Ruth D. (1995)
"Mitochondrial DNA Variation in the Yanomami of Brazil"

Levinson, Kara (1996)
"Linkage Analysis of Hereditary Lymphedema: Analysis for a Genome Scan"

Moriarty, Megan (1997)
"Genetic Variation as it Relates to Body Weight In Healthy Premenopausal Women: The TRP64 ARG Substitution of the $_3$-Adrenergic Receptor and the GLU223ARG Substitution of the Leptin Receptor"

Montoya, Susana E. (1998)
"Genetic Analysis of Human Bleomycin Hydrolase"

Dent, Karin M. (1998)
"A Population Based Study of the Relationship Between Anxiety-Related Traits and Variation in the Serotonin Transporter Gene"

Specht, Susan (1998)
"Expression of HMGI-C Protein in Normal, Benign and Malignant Human Breast Tissue"

Meyers, Carina R. (1999)
"The CHS-Family Study: Analysis of the Distribution and Frequency of Affected Siblings in a Sub-Sample of the CHS Cohort"

Balwani, Manisha C. (1999)
"Calcium Sensing Receptor Polymorphisms: Relationship with Bone Mineral Density, Serum Calcium and Parathyroid Hormone"

Yang, Zi-wei (1999)
"Cloning and Sequencing of the Rabbit FGFR2 cDNA"

Kudla, Donna M. (2001)
"Comparative Gene Expression Analysis of Ovarian Carcinoma and Human Ovarian Surface Epithelia by Serial Analysis of Gene Expression"

Dunlap, Jean W. (2002)
"Is There a Genetic Predisposition to Secondary Lymphedema in Breast Cancer Patients?"

MULTIDISCIPLINARY MPH

Winkler, Linda (2001)
"An Analysis of Genetic Diversity and Disease Prevalence on the Island of Ometepe in Nicaragua Using a Monkey Model."

DOCTOR OF PHILOSOPHY

Graduate School of Biomedical Sciences, University of Texas:

Pryor, Steven C. (1980)
Clench, Jocelyne (1980)
Friedrich, Christopher A. (1986)
Eichner, June E. (1986)

Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh:

Sepehrnia, Bahman (1988)
"The Effect of Apolipoprotein Polymorphism on Quantitative Levels of Lipids and Lipoproteins in Nigerians".

Cole, Shelley A. (1990)
"A Study of Association of RFLPs at the CETP, Apo D and LPL Loci with Levels of Plasma Lipids in an Hispanic Population".

Chidambaram, Abirami (1990)
"Role of the Retinoblastoma Gene Locus in Li-Fraumeni Syndrome".

Law, John C. (1991)
"Germ Line p53 Mutations in Familial and Childhood Cancer".

Lyons, Leslie A. (1991)
"Resolution of the Two Designated Loci, AN1 and AN2, for Autosomal Dominant Aniridia by Linkage Analysis with Chromosome 2p and 11p13 Markers".

Iyengar, Sudha (1992)
"The NIDDM Phenotype: Complex Segregation Analysis and Impact of Several Genes in Glucose Metabolism".

Merriwether, D. Andrew (1993)
"Mitochondria DNA Variation in South American Indians"

St. Jean, Pamela L. (1994)
"The Genetic Etiology of Abdominal Aortic Aneurysms"

Armitage, Marlene M. (1995)
"Mapping of the Cerulean Cataract Gene by Linkage Analysis"

Perry Conley, Yvette (1999)
"The Molecular Genetics of Autosomal Dominant Hypocalcemia"

Moffett, Susan (2001)
"The PPAR Pathway to Obesity and Type 2 Diabetes: A Multilocus Approach to Understanding Complex Disease"

Damcott, Coleen (2001)
"Genetic Variation in the Uncoupling Protein and Fatty Acid Binding Protein Gene Families: A Multi-Locus Approach to Investigating Obesity and Type 2 Diabetes"

Post-doctoral Fellows/Visiting Investigators

Name	Years	Current Position
M. I. Kamboh, Ph.D.	1985-1987	Professor University of Pittsburgh
Ranjan Deka, Ph.D.	1987-1990	Professor University of Cincinnati
C. S. Ishwad, Ph.D.	1987-1989	Research Associate University of Pittsburgh
June Eichner, Ph.D.	1987-1989	Professor University of Oklahoma
John Ely, Ph.D.	1988-1991	Scientist Bioqual, Inc.
A. Ramesh, Ph.D.	1989-1991	Professor Madras India

Mae Gailani, M.D.	1989-1990	Assistant Professor Yale University
John C. Law, Ph.D.	1992-1993	Assistant Professor Shippensburg University
Sara Huston, Ph.D.	1994-1995	Intern, Center for Disease Control and Prevention
Pamela St. Jean, Ph.D.	1994-1995	Scientist Glaxo-Wellcome Corporation
D. Andrew Merriwether, Ph.D.	1993-1996	Associate Professor Anthropology SUNY-Binghamton
Wendy Rubenstein, M.D., Ph.D.	1995-1996	Medical Director Center for Medical Genetics Evanston Northeastern Healthcare
Mark Shriver, Ph.D.	1993-1996	Assistant Professor Penn State University
Chittiwat Suprasongsin, M.D.	1996-1997	Ramathibodi Hospital Bangkok, Thialand
David Peters, Ph.D.	1995-1998	Assistant Professor University of Pittsburgh
Jeremy Martinson, Ph.D.	1996-1998	Assistant Professor University of Pittsburgh
Harry Culling, Ph.D.	1998-1999	Scientist, Radiation Effects Research Foundation Hiroshima (National Academy of Sciences)
Steve Riechman, Ph.D.	1999-2002	Assistant Professor Kent State University
Steven Roth, Ph.D.	2000-2002	Assistant Professor University of Maryland

EXTERNAL EXAMINER

Partha P. Majumder, Indian Statistical Institute, Calcutta, Ph.D., 1981.

M.I. Kamboh, Australian National University, Canberra, Ph.D., 1984.

Rodolfo Valdez, Department of Anthropology, Penn State University, Ph.D., 1990.

M. Ramesh, Department of Human Genetics, Andhra University, Ph.D., 1992.

N. Lakshmi, Department of Human Genetics, Andhra University, Ph.D., 1994.

Heng Chew Kiat, National University of Singapore, Ph.D., 1996.

See-Kiong Ng, Carnegie Mellon University, Ph.D., 1998.

Carolina Bonilla, Penn State University, Ph.D., 2001.

PUBLIC HEALTH CAREERS OPPORTUNITY SUMMER PROGRAM

Ronald Spencer, 1984
Margaret Chao, 1986
Jean M. Ou, 1991
Dion C. Camp, 1992
Nirav Chiniwalla, 1992
Janeen Stone, 1992
Neto Réid-Brossard, 1993

UNDERGRADUATE HONORS PROGRAM INTERNSHIP

José Mediavilla, 1993-1996
Nirav Chiniwalla, 1994
Nicholas Steadman, 1994
Ashadi Ahmed, 1995
Josh Akey, 1996-1998
Roxanne Miller (Chatham College) 1999-2000

QUEST (Advanced Program for Minority Undergraduates)

Kendall Horman-Cooper, 1991
Alicia Dickerson, 1993
Angela Stubbs, 1994

RESEARCH VOLUNTEERS/SHORT TERM RESEARCH VISITORS

Aubrey Watkins	1991-1993 (Dept.of Biology)
Jennifer Gross	1995-1996
Liane Daigneau	1996-1997 (Dept. Of Biology)
Mark Panna	1997
Matthew Becker	1997
Patrick Shea	1998-2000 (Dept. Of Biology)

Miryoung Lee	1998-2000 (Dept. Of Epidemiology)
Hannah Pope	1999 (Dept. Of Anthropology)
Onanong Tiyasongthong	1999 (Univ.of MD)
Burcu Guner	1999 (Turkey)
Michele Souder	1999-2001 (Rehabilitation Sci.)
Demetrios Panagiotou	2000-2002 (Carnegie Mellon Univ.)
Mark Rohlsch	2000 (Univ.of MD)
Maria Bliel	2001 (Dept. of Psychology)
Lei Liu	2001 (Dept. of Chemistry)
Anita Ramasahayam	2001-2002 (Dental Medicine, T35 Student)
Ioana Ghiu	2002 (Univ. of MD)
Hillary Keenan	2002 (Dept. of Epidemiology)
Meera Patel	2002 (Rochester Inst. Technology)
Shan Gaur	2002 (Bethel Park High School)
Joshua Yonas	2002 (Dickinson College)
J. J. Park	2002 (Univ. of MD)
Tom Obesison, M.D.	2002 (Howard University)
Eva Miljkovic	2002-2003 (Dept. of Epidelmiology)

UNIVERSITY SERVICE

Member, N.I.H. Shared Computer Executive Committee, Department of Biostatistics, GSPH, 1986-1990

Member, Subcommittee on Medical Genetics, Curriculum Committee, School of Medicine, 1986-1988

Nominating Committee, Pew Scholars Program in the Biomedical Sciences, Member, 1986

Member, Faculty Advancement Committee, Graduate School of Public Health, University of Pittsburgh, 1985-1987; 1990-1992

Chairman, Task Force on Genetics and Immunology, University of Pittsburgh, 1984-1988

Member, Biomedical Institutional Review Board, University of Pittsburgh, 1988 - 1993; Alternate member 1993-1995; Member 1995-

Member, IRB Subcommittee on Genetic Issues, 1995-1996

Member, Faculty Senate Executive Committee, Graduate School of Public Health, 1989-1994; President, 1991-1992.

Member, Committee for Review of the Core Curriculum, Graduate School of Public Health, 1989-1990.

Chairman, Curriculum Review Committee, Department of Human Genetics, Graduate School of Public Health, 1991-1992.

ACS Institutional Research Grant Review Committee, Pittsburgh Cancer Institute, 1991- 2000.

Western Psychiatric Institute and Clinic Internal Research Peer Review Committee, 1988-

Childrens Hospital of Pittsburgh Intramural Research Grant Program, Reviewer, 1991-

Member, Scientific Advisory Committee, Child Health Research Center, 1991-

Planning and Budget Committee, Department of Human Genetics, 1992-1994

Planning and Budget Committee, Graduate School of Public Health, 1992-1994.

Member, Faculty Diversity Committee, Graduate School of Public Health, 1994.

Reviewer, Competitive Medical Research Fund, University of Pittsburgh Medical Center, Office of Research Health Sciences, 1994-

Member, Internal Review Committee for the Department of Environmental and Occupational Health, Provost Subcommittee for the Evaluation of Academic Programs, 1994.

Member, UPMC Research Policy Committee, 1994-1995.

Reviewer, Disclosure of Invention, Office of Technology Transfer and Intellectual Property, University of Pittsburgh, 1995-

Reviewer, Obesity and Nutrition Research Center, Feasibility Grants Program, 1995-

Member, Health Sciences Research Committee advisory to the Associate Vice Chancellor for Research, Health Sciences, 1996-2000.

Reviewer, Pilot Study Program, Center for Research in Chronic Disorders, School of Nursing University of Pittsburgh, 1997-

Member, Steering Committee, University of Pittsburgh Cancer Institute/Magee Womens Hospital Cancer Genetics Program, 1997-1999.

Member, Scientific Advisory Group, Center for Genomic Sciences, University of Pittsburgh, 1998-2000.

Member, Internal Scientific Advisory Committee, Center for AIDS Research, University of Pittsburgh, 1997-2002.

Member, Executive Steering Committee, Obesity Nutrition Research Center, University of Pittsburgh, 1997-

Member, Pennsylvania Congressional Liaisons, Joint Steering Committee for Public Policy, 1998-2000.

Member, Planning and Implementation Committee, GSPH 50th Anniversary Celebrations, 1998-1999

Member, Deans Committee on Faculty Governance GSPH, 1998-1999.

Member, GSPH Council, 1999-2003.

Chairman, Faculty Appointments, Promotions and Tenure Committee, GSPH, 1999-2000.

Member, Chancellor's Distinguished Research Awards Committee, 1999-

Member, Search Committee, Dean, Graduate School of Public Health, 2000

Faculty, Mini-Med 2000, University of Pittsburgh

Jay L. Foster Lecture Series in Alzheimer's Disease Selection Committee, 2001-

Member, Pittsburgh Development Center, Executive Committee, 2001-

Member, Steering Committee, Center for Public Health Practice, Graduate School of Public Health, 2001-

PROFESSIONAL ACTIVITIES

Reviewer, National Science Foundation, Systematic Biology Program, Anthropology Program, and Population Biology and Physiological Ecology Program, 1985-

Reviewer: (Current)
American Journal of Human Genetics
American Journal of Physical Anthropology
Genetic Epidemiology
Human Biology
Human Heredity
Circulation
Human Molecular Genetics
American Journal of Human Biology
Human Genetics
Diabetes Care
Diabetes
Genome Research
Nature Genetics
Atherosclerosis, Thrombosis and Vascular Biology
Journal of Geriatrics

Associate Editor, American Journal of Physical Anthropology, 1980-1987

Editorial Board: Revista International de Biologia de Poblaciones Anthropologia Biologica, 1991-
Human Biology, 1994-1996.
Indian Journal of Human Genetics, 1994-
American Journal of Human Biology, 1998-
Lymphatic Research and Biology, 2002-

Member, Scientific Advisory Board, Texas Neurofibromatosis Foundation, 1983-1985.

Member, Admissions Committee, Graduate School of Biomedical Sciences, University of Texas Health Science Center, 1979-1982, Chairman, 1982

N.I.H. Ad Hoc Study Section Member and Site Visitor, Epidemiology and Disease Control and Mammalian Genetics Study Sections, 1982 - present.

Guest Lecturer, NIH Interinstitute Medical Genetics Program, Bethesda, 1985-1987.

Member, Centre d'Etude du Polymorphisme Humaine (C.E.P.H.), 1986-

Co-Chairman (with Dr. John Wasmuth), Chromosome 5 Committee, Human Gene Mapping Workshop, 1988-1989.

Co-Chairman (with Dr. V. Zannis), Apolipoprotein Genetics Session, 4th International Colloquium, Foundation for Research in Atherosclerosis, Brussels, 1988.

Member, Chimpanzee Breeding and Research Program Advisory Committee, N.I.H., 1986-1990.

Visiting Scientist, Charing Cross Sunley Research Center, London, July-December, 1990. Molecular genetics of cardiovascular disease risk factors. S.E. Humphries, Ph.D.: Sponsor.

Co-Organizer (with Dr. A. Chakravarti) Statistical Methods in Gene Mapping. October 4-6, 1991, Nemacolin, PA

Faculty Member, N.A.T.O. Advanced Research Workshop: Standardization of Epidemiologic Studies of Host Susceptibility, 1992.

Ad Hoc Reviewer, Wenner-Gren Foundation for Anthropological Research, 1991-1993.

Moderator, Physical Mapping of Cosmids YACs, STSs and Expressed Sequences, First International Human Chromosome 13 Workshop, Dallas, 1992.

Session Organizer and Chair. Genetic Studies of Human Populations. Haldane Centenary Celebrations. Indian Statistical Institute, Calcutta, 1992.

Consultant (unpaid), Commonwealth of Pennsylvania, Greensburg Regional Laboratory, Forensic DNA Laboratory, 1991- 1999.

Lecturer, Medical Genetics Board Review Course, Pittsburgh, PA, 1993.

Reviewer, Allegheny-Singer Research Institute, Scientific Project Proposal Review Panel, 1995-1998.

Member, Bogalusa Heart Study Advisory Group, School of Public Health and Tropical Medicine, Tulane University Medical Center, 1996-1997.

Scientific Review Panel, National Health and Nutrition Examination Survey, National Center for Health Statistics, 1997.

Member, National Cancer Institute, Intramural Scientific Review, Ad hoc Reviewer, 1999.

Member, Scientific Advisory Board, Gene Survey project Biological Anthropology Laboratory, University of Maryland (Fatimah Jackson, Ph.D., Director)/2000-

Co-Chair, Task Force on Genetics and Development, *Conquering Lymphatic Disease: Setting the Research Agenda*, N.I.H., 2000.

Member, Scientific Advisory Board, Lymphedema Research Foundation, 2000-

Member, Scientific Advisory Committee, Center for Environmental Health Sciences, University of Montana, Missoula, MT, 2000-.

Reviewer, McAbee Fellowship Grant, Diabetes Endocrinology Research Center, University of Washington, Seattle, 2001.

External Reviewer, Ohio Eminent Scholars Program, Ohio Board of Regents, 2001.

Chairman, Genetics Working Group advisory to the NHLBI BARI 2D clinical trial, 2001-.

Member, Conference Steering Committee, EPA Conference on Biological Variability in Children and Implication for Environmental Risk Assessment: New Perspectives on the Roles of Ethnicity, Race and Gender. September, 2001, College Park, MD

Member, National Advisory Board, New York African Burial Ground Project, 2000-

Reviewer, Health Research Board, Ireland, 2001.

Member, American Heart Association Mid-Atlantic Consortium Peer Review Group, 2001-

Reviewer, Guy's and St. Thomas Charitable Foundation Research Training Award Program, 2002

Reviewer, Sheffield Hospitals Charitable Trust, Medical Research Committee, 2002.

Member, Age, Genes, Environment and Susceptibility (AGES) Study of the Reykjavik Study of Healthy Aging for the New Millennium, 2002-

REFEREED ARTICLES

1. **Ferrell RE**, Kitto GB: Properties of Dendrostomum pyroides hemerythrin. *Biochem* 1970; 9:3053.

2. **Ferrell RE**, Kitto GB: The aminoterminal sequence of Dendrostomum pyroides hemerythrin. *FEBS Letters* 1971; 12:322.

3. **Ferrell RE**, Kitto GB: Structural studies on Dendrostomum pyroides hemerythrin. *Biochem* 1971; 10:2923.

4. Tashian RE, Tanis RJ, **Ferrell RE**, Stroup SK, Goodman M: Differential rates of evolution in the carbonic anhydrase isozymes of catarrhine primates. *J Hum Evol* 1972; 1:545.

5. Tanis RJ, **Ferrell RE**, Tashian RE: Substitution of lysine for threonine 100 in human carbonic anhydrase Id Michigan. *Biochem Biophys Res Comm* 1973; 51:699.

6. Carter ND, Tanis RJ, Tashian RE, **Ferrell RE**: Characterization of a new variant of human red cell carbonic anhydrase I, CA If London (102 Glu to Lys). *Biochem Genet* 1973; 10:399.

7. Tanis RJ, **Ferrell RE**, Tashian RE: Amino acid sequence of sheep carbonic anhydrase C. *Biochem Biophys Acta* 1974; 371:534.

8. Tanis RJ, **Ferrell RE**, Neel JV, Morrow M: Albumin Yanomama-2, a "private" polymorphism of serum albumin. *Ann Hum Genet* 1974; 38:179.

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GRANT SUPPORT (Last 5 years)

N.I.H., RO1 HL44682Genetic Basis of Abdominal Aortic Aneurysm. NIH/NHLBI, R. E. Ferrell, Principal Investigator, 12/01/90-11/31/01, $200,000 annual direct costs.

N.I.H., R01 HL39107, Genetic Epidemiology of Coronary Heart Disease. NIH/NHLBI, 7/1/87-6/30/01, C.F. Sing, Principal Investigator, R.E. Ferrell, Coinvestigator, $91,000 annual direct costs.

*N.I.H., RO1 EY09859, Genetics of Age Related Maculopathy. M.B. Gorin, Principal Investigator, R.E. Ferrell, Coinvestigator, 8/1/93-7/31/03, $270,000 annual direct costs.

N.I.H., RO1 HL32197, Markers of Family History of CAD in the Young. C.F. Sing, Principal Investigator, R.E. Ferrell, Coinvestigator, 8/1/94-7/31/99, $260,000 annual direct costs (University of Pittsburgh: $67,095 annual direct costs.)

*N.I.H., U10 HL54526, Genetic Determinants of High Blood Pressure in Three Racial Groups. R.E. Ferrell, Principal Investigator, 10/01/95-09/30/05, $200,000 annual direct costs.

N.I.H., 1RO1 DK49632, Genetic Epidemiology of NIDDM in an Hispanic Community. C. E. Aston, Principal Investigator, R. E. Ferrell, Coinvestigator, 6/1/95-5/31/99, $90,000 annual direct costs.

N.I.H., RO1 HL45778, Genetic Epidemiology of Blood Lipids and Obesity. NIH/NHLBI, S. Y. Kimm, Principal Investigator, R. E. Ferrell, Coinvestigator, 01/01/93-07/31/99, $200,000 annual direct costs.

N.I.H., P50 AG05133, Alzheimers Disease Research Center: Project 2: Genetic Epidemiology of Alzheimer's Disease. R. E. Ferrell, P.I., 05/01/95-04/30/00, $62,000 annual direct costs.

*N.I.H., RO1 AG15389, APOE Genotype and HDL Changes with Exercise Training. James Hagberg, P.I., R.E. Ferrell, Coinvestigator, 06/01/98-05/31/03, $244,160 annual direct costs.

N.I.H., R21 AG16205, Genotype, Age, Muscular Strength and Muscle Mass. B.F. Hurley, P.I., R.E. Ferrell, Coinvestigator, 12/01/98-11/30/00, $99,080 annual direct costs.

*N.I.H., R1 DK34818, Epidemiology of Diabetic Complications-Phase II. T.J. Orchard, P.I., R.E. Ferrell, Coinvestigator, 04/01/99-03/31/03, $500,000 annual direct costs.

DAMD17-99-1-901, DOD, Tobago Prostate Cancer Survey. Clareann Bunker, P.I., R.E. Ferrell, Coinvestigator, 11/02/98-06/01/01, $100,000 annual direct costs.

*N.I.H., RO1 CA84950, Molecular Epidemiology of Prostate Cancer in Tobagonians. Clareann Bunker, P.I., R.E. Ferrell, Coinvestigator, 10/01/99-09/30/04, $400,000 annual direct costs.

*N.I.H., RO1 AG17474, ACE Genotype, Blood Pressure and Exercise Training in Hypertensives. James Hagberg, P.I., Robert Ferrell, Coinvestigator, 10/01/00-09/30/05, $300,000 average annual direct costs.

*N.I.H., RO1 MH59792, Neurogenetics, Serotonin and Human Aggression. Stephen Manuck, P.I., Robert Ferrell, Coinvestigator, 10/01/00-09/30/05, $260,000 average annual direct costs.

*N.I.H., RO1 DA11922, Substance Abuse and Dopamine System Genes. Michael Vanyukov, P.I., Robert Ferrell, Coinvestigator, 12/01/99-11/30/04, $350,000 average annual direct costs.

*N.I.H., RO1 HD37243, Genetic Studies of Lymphedema. David N. Finegold, P.I., Robert E. Ferrell, Coinvestigator, 07/01/00-06/30/03, $250,000 annual direct costs.

*N.I.H., RO1 AG18336, Gene Effects on Strength Responses to Age and Exercise. B.F. Hurley, P.I., R.E. Ferrell, Coinvestigator, 12/01/01-11/30/06, $300,000 annual direct costs.

*N.I.H., RO1 HL66070, Genetic Epidemiology of Energy Metabolism in Black Girls. S.Y.S. Kimm, P.I., R.E. Ferrell, Coinvestigator, 05/01/01-04/30/05, $360,000 annual direct costs.

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* Active support

Common Name	IUBMD Nomenclature	Sequence Specificity	Reference
Cathepsin B	EC3.4.22.1	X-X-Arg-Arg-X	1
Chymase	EC3.4.21.39	X-X-Phe-X-X[2] X-X-Tyr-X-X X-X-Trp-X-X X-X-Leu-X-X	2
Chymotrypsin A	EC3.4.21.1	X-X-Tyr-X-X X-X-Trp-X-X X-X-Phe-X-X X-X-Leu-X-X	3
Elastase 1	EC3.4.21.36	X-X-Ala-X-X	4
Furin	EC3.4.21.75	Arg-X-Arg-Arg-X Arg-X-Lys-Arg-X	5
Plasmin	EC3.4.21.7	X-X-Lys-X-X X-X-Arg-X-X	6
Thermolysin	EC3.4.24.27	X-X-Leu-X-X X-X-Phe-X-X	7
Thrombin	EC3.4.21.5	X-X-Arg-Gly-X-X	8
Trypsin	EC3.4.21.4	X-X-Arg-X-X X-X-Lys-X-X	9

1 : X = any amino acid
2 : Sequences listed in order of substrate preference

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Perspectives in Diabetes

Hexosamines and Insulin Resistance

Donald A. McClain and Errol D. Crook

Glucose is an important regulator of cell growth and metabolism. Thus, it is likely that some of the adverse effects of hyperglycemia are reflections of normal regulation by abnormal concentrations of glucose. How the cell senses glucose, however, is still incompletely understood. Evidence has been presented that the hexosamine biosynthesis pathway serves this function for regulation of aspects of glucose uptake, glycogen synthesis, glycolysis, and synthesis of growth factors. Excess hexosamine flux causes insulin resistance in cultured cells, tissues, and intact animals. Further evidence for the possible role of this pathway in normal glucose homeostasis and disease is that the level of activity of the rate-limiting enzyme in hexosamine synthesis, glutamine:fructose-6-phosphate amidotransferase, is correlated with glucose disposal rates (GDRs) in normal humans and transgenic mice. *Diabetes* **45:1003–1009, 1996**

ADVERSE EFFECTS OF HYPERGLYCEMIA: TOXICITY VERSUS DYSREGULATION

The results of several clinical studies, most recently the Diabetes Control and Complications Trial, convincingly demonstrate that hyperglycemia is the cause of most if not all of the chronic complications of diabetes (1). In addition to these mainly vascular problems, hyperglycemia can also have adverse consequences for glucose homeostasis itself (2,3). These changes are part of a vicious cycle that worsens the diabetic state and makes glycemic regulation more difficult. At the level of the pancreatic β-cell, there is evidence that hyperglycemia itself can lead to many of the defects in insulin secretion that are observed in NIDDM (4–6). Hyperglycemia also worsens insulin resistance (2,7,8), and resistance improves upon attaining tight control of diabetes (6). In vitro, adipocytes exposed to high concentrations of glucose develop impaired insulin signaling and responsiveness and recruit fewer glucose transporters to the plasma membrane in response to insulin (9,10). Muscle glycogen synthase activity can also be affected by hyperglycemia (11,12). Thus, hyperglycemia interferes widely with cellular metabolism and the mechanisms for insulin-induced glucose disposal.

Such adverse metabolic consequences of hyperglycemia have been referred to as glucose toxicity (6). There have been several hypotheses proposed for the biochemical basis for glucose toxicity, and any of the several proposed mechanisms may contribute to pathology in different cells or tissues. For example, high concentrations of glucose might damage cells through nonenzymatic glycation of proteins and the accumulation of advanced glycation end products (13,14). Other theories on the mechanism of glucose toxicity have considered the accumulation in cells of normal products of glucose metabolism, but at higher than normal concentrations. Sorbitol accumulates in diabetic nervous tissue (15,16), and excess glucose can also lead to the accumulation in cells of diacylglycerol, an activator of protein kinase C (PKC) that could have wide-ranging effects on cellular regulation (17,18).

Glucose is also known to be an important regulator of normal cell growth and metabolism. Therefore, it may be useful to distinguish "toxic" effects from normal regulatory or desensitizing effects, as has been pointed out by Robertson et al. (19). Some of the consequences of hyperglycemia can be well understood as toxic in the classic sense, such as the nonenzymatic glycation of proteins. On the other hand, some of the adverse results of hyperglycemia might be caused by normally functioning regulatory pathways. The fact that excessive glucose flux through its normal metabolic pathways rather than hyperglycemia per se can have adverse consequences has been demonstrated with mice overexpressing the GLUT1 glucose transporter (20). Increased glucose flux into skeletal muscle leads to insulin resistance in these mice despite the fact that they have somewhat lower than normal serum glucose levels. In the presence of excess glucose, protective mechanisms should exist that prevent cellular overfeeding and shunt glucose toward chronic storage pathways. Such changes—blunting of insulin-stimulated glucose uptake and glycogen synthesis, downregulation of glucose transporters in sensitive tissues, and increases in the synthesis of fatty acids and triglycerides, for example—might be protective of cells and tissues over periods of hours to days but maladaptive to the organism in conditions of chronic hyperglycemia or caloric excess.

How cells sense glucose flux so that they may regulate their metabolism according to the availability of fuel is largely unknown, although it is generally agreed that glucose metabolism is required for such effects. At the simplest level, some glucose metabolites act as allosteric regulators of key

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DON, diazo-oxo-norleucine; F6P, fructose-6-phosphate; GDR, glucose disposal rate; GFA, glutamine:fructose-6-phosphate amidotransferase; GlcNAc, *N*-acetylglucosamine; PKA, protein kinase A; PKC, protein kinase C; PP1, protein phosphatase 1; TGF-α, transforming growth factor α; UDP, uridine diphosphate; UTP, uridine triphosphate.

EXHIBIT B

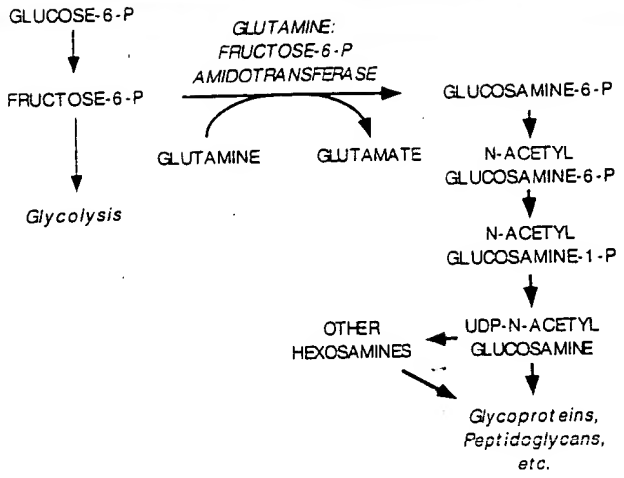

FIG. 1. The hexosamine biosynthesis pathway.

enzymes in glycolytic, glycogenic, and gluconeogenic pathways. The stimulation of insulin secretion by glucose has been hypothesized to be the result of changes in ADP/ATP ratios brought about by graded flux down the glycolytic pathway, ultimately controlled by the relatively low affinities for glucose of the glucose transporter GLUT2 and glucokinase in the β-cell (21,22). Nevertheless, other evidence is difficult to reconcile with the ADP/ATP ratio hypothesis, and the more subacute sensing of glucose flux such as is responsible for the regulation of insulin gene transcription probably operates through a different mechanism (23–25). The identification of carbohydrate response elements in several genes should ultimately lead to the clarification of these mechanisms (26). At the present time, however, the identity of the metabolic pathways through which cells are made aware of and respond to fuel availability remains unknown. Given the importance of glucose for cell growth and metabolism from prokaryotes to humans, it is not unlikely that glucose sensing and regulation may have evolved to operate through more than one mechanism.

THE HEXOSAMINE PATHWAY AND INSULIN RESISTANCE: IN VITRO STUDIES

It has recently been shown that at least some of the regulatory effects of glucose are mediated by the hexosamine biosynthesis pathway, in which fructose-6-phosphate (F6P) is converted to glucosamine-6-phosphate, with glutamine acting as the donor of its amido group (Fig. 1). The final products of the pathway are uridine diphosphate (UDP)-*N*-acetyl-glucosamine (GlcNAc) and other nucleotide hexosamines. The amination of F6P is rate limiting—except in cases of very high flux, in which case uridine triphosphate (UTP) may be limiting (27)—and is catalyzed by glutamine: F6P amidotransferase (GFA or GFAT). This enzyme in eukaryotes is subject to feedback inhibition by UDP-GlcNAc and can be experimentally inhibited by glutamine analogs such as azaserine or diazo-oxo-norleucine (DON).

The first to implicate the hexosamine pathway in cellular regulation were Marshall et al. (28), who were studying glucose transport in cultured adipocytes exposed to high concentrations of glucose. A serendipitous finding that glutamine was a required cofactor for glucose-induced desensitization of the insulin-stimulated glucose transport system prompted a series of systematic and elegant experiments that resulted in the hypothesis that hexosamine metabolism might be involved. Glucosamine was found to be many times more potent than glucose in inducing insulin resistance and decreased insulin responsiveness. Marshall was able to block the ability of glucose to induce insulin resistance by inhibiting GFA, and glucosamine was able to bypass that blockade. He therefore hypothesized that hexosamine metabolism may be the pathway by which cells sense and respond to the ambient glucose levels and, when glucose flux is excessive, downregulate glucose transport and become insulin resistant (28). Later studies from Marshall's laboratory strengthened the hypothesis and currently support the idea that glucosamine flux results in transcriptional regulation of a number of genes relevant to glucose homeostasis (see below).

Several other laboratories have subsequently examined the effects of hexosamines on glucose homeostasis. Robinson et al. (29) showed that preexposure to glucosamine induced insulin resistance in skeletal muscle, the tissue responsible for the majority of insulin-dependent glucose utilization. Incubating rat hemidiaphragms in 5–22 mmol/l glucosamine resulted in a 20–60% reduction in basal glucose transport and a significant reduction in the ability of insulin to increase glucose transport (29). They hypothesized that the decrease in glucose transport was secondary to altered translocation of the GLUT4 transporter because the total GLUT4 pool was not affected by glucosamine. Moreover, they showed that preexposure to glucosamine abolished the ability of insulin to stimulate glycogen synthesis but that insulin stimulation of glycogen synthase and insulin receptor number/activation were not affected. In contrast to these results, in L_6 myotubes, hexosamine biosynthesis had no effect on glucose regulation of glucose transport (30); the different results of these studies may be explained by the fact that glucose transport in L_6 myotubes is mediated by GLUT1 rather than GLUT4.

To avoid the possible side effects of treating cells with high concentrations of glucosamine and to implicate the hexosamine pathway more directly in glucose homeostasis, our laboratory has taken a transgenic approach to modifying intracellular hexosamine biosynthesis. Initially, the yeast cDNA for GFA was isolated and transfected into Rat-1 fibroblasts by electroporation. Cells overexpressing GFA were insulin resistant, as demonstrated by a rightward shift in the dose-response curve for insulin-stimulated glycogen synthase activity (31). The cells that overexpressed GFA did not exhibit changes in total glycogen synthase activity (an indirect measure of enzyme mass), maximal insulin-stimulated activity (insulin responsiveness), or insulin binding and receptor number. Thus, the defect in insulin signaling appeared to be a postreceptor one. Glucose uptake, mediated mainly by GLUT1 in these cells, was also unaffected by overexpression of GFA.

Subsequently, we were able to stably overexpress the human cDNA for GFA (32,33) in Rat-1 fibroblasts to facilitate further mechanistic studies of how hexosamine metabolism regulates glycogen synthesis (34). The increase in the levels of GFA that we were able to achieve in our transfectants was modest, on the order of twofold. Despite this, cells stably overexpressing GFA were insulin resistant for the stimulation of glycogen synthase activity. Basal glycogen synthase activity and insulin sensitivity were both decreased by treatment of the cells with high concentrations (10–20 mmol/l) of glucose, and this decrease in basal synthase activity was

observed at lower glucose concentrations in cells overexpressing GFA. GFA overexpression also accentuated the effects of high glucose on insulin sensitivity (35). These results support the hypothesis that glucose sensing for the regulation of insulin-stimulated glycogen synthase does operate through the hexosamine biosynthesis pathway.

Glycogen synthase, the rate-limiting enzyme in glycogen synthesis, is regulated through a complex cascade of protein kinases and phosphatases. The activity of glycogen synthase is determined by the phosphorylation state of the enzyme and is under hormonal control (36). The enzyme can be phosphorylated at multiple sites by >10 protein kinases (37) that in general inhibit enzyme activity (38). Insulin activates glycogen synthase by stimulating its dephosphorylation (39–41). An insulin-stimulated protein kinase has been shown in vitro to phosphorylate and activate PP1G (41), the glycogen-bound form of type-1 protein phosphatase. In cells overexpressing GFA, we found PP1 to be downregulated by glucose. Glucosamine downregulates basal PP1 activity with greater potency than glucose, and both glucosamine and high glucose significantly reduce insulin's ability to stimulate PP1 (35). In contrast, mitogen-activated protein (MAP) kinase and S6 kinase, intermediates in the insulin signaling cascade, have been shown not to be affected by glucosamine in rat fibroblasts (29). Similarly, we have seen no alterations in S6 kinase activity in cells overexpressing GFA (E. Crook, unpublished observations). Taken together, these data show that hexosamines regulate glycogen synthase by regulating its phosphorylation state. This regulation appears to occur more distally in the insulin signaling cascade, and the relatively slow time course of the regulation suggests a transcriptional mechanism.

Other enzymes and proteins involved in glucose disposal have also been shown to be regulated by hexosamine metabolism in vitro. These include pyruvate kinase (42), glycogen synthase in rat adipocytes (43), and GLUT1 in bovine retinal capillary pericytes (44). An important goal for future research, therefore, is to define the extent and generality of the regulation of metabolism through this pathway.

HEXOSAMINES AND INSULIN RESISTANCE IN VIVO

Diabetes is a disease of the whole animal, and although there are in vitro models for aspects of diabetes, ultimate proof of any mechanism in that disease requires its demonstration in the intact organism. The effects of excess hexosamines in intact animals were first studied by Rossetti et al. (45). Rats were infused for 7 h with glucosamine, resulting in plasma glucosamine concentrations of ~1.2 mmol/l. Euglycemic-hyperinsulinemic glucose clamp studies were then performed to measure GDRs under conditions in which hepatic glucose output was suppressed. Glucosamine infusion resulted in a 31% decrease in GDRs in normal animals, but glucosamine led to no further reduction in the suppressed glucose disposal observed in partially pancreatectomized diabetic rats. The latter fact demonstrates that hyperglycemia and glucosamine are nonadditive; that is, they probably operate through the same pathway to cause decreased glucose disposal. Muscle glycogen synthase activity was unaffected by the glucosamine infusion, in contrast to the results obtained by Crook et al. (31) in cultured fibroblasts. Whether this difference is due to the cell type examined or to the relatively short-term glucosamine infusion is not known.

More recently, Baron et al. (46) observed similar results in rats infused with glucosamine at a rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$, or 1/70th of the molar rate of glucose uptake (46). They were able to demonstrate that glucosamine impaired the translocation of the insulin-stimulated glucose transporter GLUT4 similarly to what is observed in human insulin-resistant states. As was the case in the previous study, these experiments were performed in animals infused with maximal concentrations of exogenous insulin, an important point because glucosamine is an inhibitor of glucokinase and has been shown to interfere with β-cell glucose sensing and endogenous insulin secretion (47).

The metabolic fate of infused glucosamine is important to consider in the interpretation of these studies. Glucosamine enters the cell through the glucose transporters and is then phosphorylated by hexokinase. The K_m for uptake of glucosamine is approximately three times that of glucose (E. Crook, unpublished observations), and the affinity of hexokinase for glucosamine is decreased to a similar degree compared with glucose. Thus, the concentrations of glucosamine achieved in the blood of infused animals are probably not sufficient to cause their effects by competing for glucose uptake or metabolism. However, glucosamine has negligible blood concentrations in animals, diabetic or not, and in order to force enough glucosamine through the hexosamine biosynthesis pathway, clearly nonphysiological concentrations of glucosamine are required. When exposed to concentrations of glucosamine in the millimolar range, cellular levels of UTP can be depleted because of increased rates of nucleotide-hexosamine formation (27). This could lead to marked changes in intracellular glucose utilization, for example if UTP became no longer available for UDP-glucose and subsequent glycogen synthesis (29). At these concentrations of glucosamine, protein glycosylation is also inhibited.

For these reasons, we have performed analogous experiments in a situation where there would less likely be large shifts in substrate fluxes. Namely, we have overexpressed GFA in transgenic animals at approximately twofold increased levels. Thus, the hexosamine pathway that normally accounts for perhaps 2% of total cellular glucose flux (28) might now account for 4–6%, a level that should not significantly alter glucose availability for oxidative or nonoxidative metabolism. In cultured cells, these levels of chronic GFA overexpression did not alter nucleotide triphosphate concentrations but did result in an approximately twofold increase in the levels of UDP-hexosamines. GFA was targeted to the two principal tissues for insulin-mediated glucose disposal, striated muscle and fat, using the promoter for the glucose transporter GLUT4. Two independent founder lines with 1.5- to 2.3-fold increased levels of GFA activity in extracts of both fat and muscle were analyzed. Fasting glucose and insulin levels were not different from the controls, the predicted result based on the specific targeting of the gene to muscle and fat and not to the liver. That is, hepatic glucose output is presumably normal, and only insulin-mediated glucose disposal into its target tissues should have been affected. Indeed, random-fed animals were hyperinsulinemic, and the insulin-to-glucose ratio was significantly elevated in the fed transgenics (48). The hyperinsulinemia was age- and weight-dependent, becoming statistically significant at 6 months and in animals >30 g, a phenotype reminiscent of NIDDM. The suggestion of insulin

resistance based on the elevated insulin-to-glucose ratios was confirmed by the use of the euglycemic-hyperinsulinemic clamp technique (20 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin, glucose levels clamped at 125 ± 15 mg/dl). Transgenic animals exhibited a significant 48% decrease in GDR compared with age- and weight-matched littermate controls. The 20 mU insulin concentration resulted in maximal glucose disposal and near total suppression of hepatic glucose output. Whether these mice can serve as an accurate model for human diabetes or glucose toxicity is currently under investigation.

HEXOSAMINES AND REGULATION OF CELL GROWTH

Other evidence also links the hexosamine pathway to glucose-induced changes in cell growth. It has been shown that glucose, through its metabolism to glucosamine, can affect the regulation of the gene for transforming growth factor α (TGF-α) in cultured vascular smooth muscle cells (49,50). Glucose was shown to stimulate the level of TGF-α mRNA in primary cultures of rat aortic smooth muscle cells approximately twofold, whereas glucosamine at lower concentrations stimulated mRNA levels six- to sevenfold. GFA overexpression mimicked the effects of high glucose on TGF-α expression (50), and these effects were abolished by inhibitors of GFA. Importantly, the effects of sugars and of GFA overexpression on TGF-α were nonadditive, arguing that glucose and glucosamine did exert these effects through the hexosamine pathway. Studies with phorbol esters to pharmacologically stimulate or downregulate PKC and with various stimulators of cAMP-dependent pathways gave no evidence to support PKC or cAMP as mediators of these effects.

More recent work has focused on the growth factor TGF-β. TGF-β, which is not structurally related to TGF-α, has been implicated in the pathogenesis of diabetic nephropathy. TGF-β can cause increased cell matrix synthesis in vitro and glomerulosclerosis in vivo, and the protein is known to be upregulated by glucose (51). The question has therefore been asked whether this glucose regulation might also be based on hexosamine flux, and the preliminary indications are that it would appear to be so. Namely, glucosamine has been shown to be more potent than glucose in stimulating TGF-β transcription in cultured renal glomerular and proximal tubule cells (52). Such results may therefore link the hexosamine pathway not only to the metabolic abnormalities of hyperglycemic states but to chronic vascular complications of diabetes as well. Besides the involvement of TGF-β in diabetic nephropathy, growth factors such as platelet-derived growth factor, fibroblast growth factor, and TGF-β have also been implicated in the development or progression of atherosclerosis. Glucose-induced stimulation of these growth factors may be part of the explanation of the increased risk of vascular disease in diabetes.

POSSIBLE MECHANISMS FOR EFFECTS OF HEXOSAMINES

How alterations in hexosamine flux might regulate metabolism is unknown. The effects of glucosamine infusions into rats to cause insulin resistance and defects in glucose uptake occur very rapidly, suggesting posttranslational mechanisms. On the other hand, the effects of glucosamine on TGF-α are clearly transcriptional (49,50), and indirect pharmacological data on the desensitization of the glucose transport system in adipocytes suggested the same (53).

Production of the substrates for protein glycosylation by the hexosamine pathway suggests a possible mechanism for the regulatory effects of hexosamines. Recently, a pathway in which intracellular proteins are modified by the O-linked addition of single GlcNAc residues has been described (54). This cytosolic O-glycosylation is a widespread event that occurs reciprocally with phosphorylation and is highly dynamic and regulated, occurring with mitogenic stimulation of lymphocytes and in G_1 phase of the cell cycle (55). All of the proteins that have been found to be modified by O-linked addition of GlcNAc are multimeric, leading to the possibility that this modification may be important in regulating the assembly of large protein complexes such as occur in cytoskeletal and transcriptional assemblies. Several transcription factors are O-glycosylated (56), and the functional consequences of O-glycosylation to their assembly into active complexes are currently being studied in several laboratories. c-*myc*, for example, has been recently shown to be O-glycosylated at a known phosphorylation site, lending credence that glycosylation may be a regulatory modification (57). Glucose-responsive elements from several mammalian genes have been identified, and interestingly, these include *myc*-like response elements (26). Our current hypothesis, which is still speculative, is based on the studies of insulin-stimulated glycogen synthase in cells overexpressing GFA. It is that hexosamines will act as glucose sensors by transcriptionally modulating key regulators of cellular metabolism such as the serine/threonine phosphatases involved in insulin signaling of glycogen synthesis. Such action at one or more key nodes in the pathways regulating metabolism in cells would result in global changes in glucose flux that would allow a cell to adapt to satiety, e.g., with downregulation of glucose uptake and coordinated changes in glycogen synthesis, glycolysis, and fat metabolism.

REGULATION OF HEXOSAMINE BIOSYNTHESIS

Taken together, the data reviewed above support the hypothesis that metabolism of glucose through the hexosamine pathway has a number of effects relevant to cellular growth and metabolism. It is therefore important to understand in detail the regulation of the hexosamine pathway and its influence on other metabolic pathways. The bacterial, yeast, and human cDNAs for GFA have been cloned, and structure-function analysis of the bacterial and yeast enzymes has begun. It is known that in eukaryotes GFA activity is allosterically inhibited through feedback by the downstream product of hexosamine metabolism, UDP-GlcNAc (58). In fungi, the ability of the enzyme to be feedback inhibited is developmentally regulated (59). During germination, when uninhibited synthesis of cell wall constituents including UDP-GlcNAc would be desirable, GFA loses its feedback inhibition. During sporulation, the enzyme regains its feedback inhibition, correlated with increased phosphorylation of a protein that copurifies with GFA activity. In vitro, a similar change in feedback inhibition could be induced with cAMP-dependent kinase (protein kinase A [PKA]). Thus, there is evidence that posttranslational regulation of GFA occurs in an important physiological setting. Human GFA has two consensus PKA phosphorylation sites in the "hinge" region between the NH_2-terminal amidohydrolase and the

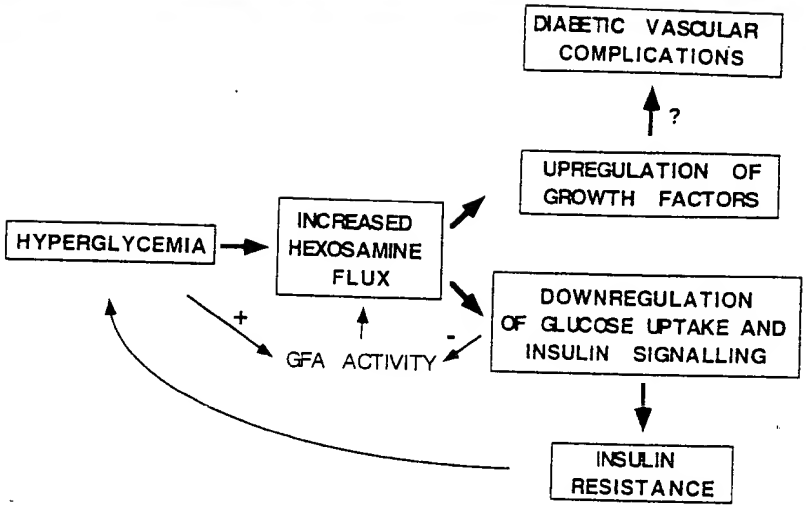

FIG. 2. Proposed role of the hexosamine biosynthesis pathway in mediating effects of chronic hyperglycemia. Excess flux through the pathway has been shown to result in insulin resistance in a number of systems, both in vitro and in vivo. This insulin resistance (and impaired β-cell function) triggered by hyperglycemia has been termed glucose toxicity and results in a vicious cycle of higher levels of glycemia leading to worse insulin resistance. The hexosamine pathway has also been implicated in the regulation of various growth factors by glucose. One of these, TGF-β, has been proposed to be directly related to the expansion of extracellular matrix and pathogenesis of diabetic nephropathy. The rate-limiting enzyme in hexosamine synthesis, GFA, is subacutely upregulated by glucose and insulin. This upregulation may serve to counter the decreased glucose flux resulting from the insulin resistance and downregulation of glucose transport. Thus, in chronic hyperglycemia, pressure would be maintained on the system to keep glucose uptake downregulated even after net glucose flux into the cell had been normalized.

COOH-terminal aldose isomerase domains, and pharmacological data suggest that human GFA is modulated by cAMP-dependent pathways (60).

Both insulin and glucose upregulate GFA activity modestly (approximately twofold) in cultured human muscle cells (61), and prolonged treatment with epidermal growth factor upregulates GFA transcription in a human breast cancer cell line (62). GFA activity in freshly obtained muscle biopsy specimens is higher in NIDDM patients compared with control subjects, and the increase in activity was correlated with glycohemoglobin levels (63). This difference between diabetic and control subjects was not seen in muscle cells cultured ex vivo, in conditions of controlled glucose and insulin concentrations (61), suggesting that the difference is secondary to hyperglycemia and/or hyperinsulinemia in the diabetic subjects. In rats, acute hyperglycemia did not affect GFA activity, whereas in chronic hyperglycemia—streptozotocin diabetic animals—GFA activity decreased (64). Insulin reversed those changes that were not associated with changes in GFA mRNA levels. The reasons for the partial discordance between the rat and human data are not clear. It must be remembered, however, that if GFA is regulated by glucose, it is intracellular glucose flux that is responsible; hyperglycemia will not correlate directly with the rates of total glucose entry into cells because of concommitant downregulation of glucose transport. It is this fact that may explain the somewhat surprising upregulation of GFA by glucose and insulin: The upregulation may serve as a compensatory mechanism to maintain total hexosamine flux in the face of the downregulation of glucose uptake (Fig. 2 and below).

RELATION OF HEXOSAMINE METABOLISM TO HUMAN DISEASE

The finding that increased GFA activity in transgenic mice leads to insulin resistance and decreased insulin-stimulated glucose uptake suggests a possible glucose-sensing role for the hexosamine pathway in the control of glucose homeostasis. This hypothesis is supported by the study of GFA levels in human muscle cell cultures. GFA levels were measured in vitro in these explanted cultured cells after 2–3 months in controlled culture conditions. GFA activity was significantly and negatively correlated with GDRs measured in vivo during a euglycemic-hyperinsulinemic clamp (61). The direction of the correlation of higher GFA being associated with lower GDR—is consistent with the transgenic mouse data and suggests a causal connection between hexosamines and glucose homeostasis. GFA activity is also correlated with obesity (61); this in part may simply restate the correlation between GFA and GDR, since obesity is so well correlated with GDR.

In NIDDM subjects, a different picture emerged (61). Namely, GFA is *positively* correlated with GDR in this group. This suggests that although basal GFA activity may be normal in NIDDM, the link between the generation of glucosamine-6-phosphate and the response to the hexosamine flux (downregulation of glucose transport, for example) may be altered in that disease. Future studies of the activity of this pathway in NIDDM are clearly indicated.

CONCLUSION

All of these studies suggest that hexosamine flux is related to glucose homeostasis and may be used for sensing extracellular glucose so that the cell can respond pleiotropically and adaptively to satiety (Fig. 2). The fact that the hexosamine pathway also utilizes glutamine as a substrate and that the K_m values for both F6P and glutamine are relatively high (in the millimolar range [58]) would allow this pathway to serve not only as a carbohydrate sensor but perhaps as a more general nutrient sensor as well. The regulatory changes signaled by this pathway may be adaptive in the short term, perhaps protecting muscle cells from excessive glucose entry or shunting surplus fuel to storage. In cases of chronic hyperglycemia or chronic caloric excess, however, these same adaptations may be reflected in some of the abnormalities of metabolism associated with the diabetic state, especially insulin resistance. The upregulation of growth factors through this pathway might also contribute to diabetic vascular complications. Finally, the altered relationship between GFA activity and glucose homeostasis in NIDDM suggests that the pathway might contribute to the underlying cause of insulin resistance as well. Future studies will be aimed at understanding the generality of metabolic regulation through the hexosamine pathway, the mechanisms by which hexosamines exert their regulatory effects, and their relation to disease states.

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[General] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

General information about the entry

Entry name	GNA1_YEAST
Primary accession number	P43577
Secondary accession numbers	None
Entered in SWISS-PROT in	Release 32, November 1995
Sequence was last modified in	Release 32, November 1995
Annotations were last modified in	Release 41, June 2002

Name and origin of the protein

Protein name	Glucosamine-phosphate N-acetyltransferase
Synonyms	EC 2.3.1.4 Phosphoglucosamine transacetylase Phosphoglucosamine acetylase
Gene name	GNA1 or PAT1 or YFL017C
From	Saccharomyces cerevisiae (Baker's yeast) [TaxID: 4932]
Taxonomy	Eukaryota; Fungi; Ascomycota; Saccharomycotina; Saccharomycete Saccharomycetales; Saccharomycetaceae; Saccharomyces.

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Barrell B.G., Churcher C., Rajandream M.A.;

EXHIBIT C

Submitted (SEP-1994) to the EMBL/GenBank/DDBJ databases.

Comments

- *CATALYTIC ACTIVITY*: Acetyl-CoA + D-glucosamine 6-phosphate = CoA + N-acetyl-D-glucosamine 6-phosphate.
- *PATHWAY*: SECOND STEP OF UDP-N-ACETYLGLUCOSAMINE (UDP-GLCNAC) BIOSYNTHESIS FROM FRUCTOSE-6-PHOSPHATE.
- *SIMILARITY*: BELONGS TO THE ACETYLTRANSFERASE FAMILY. GNA1 SUBFAMILY.

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Cross-references

EMBL	AB017626; BAA36495.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] D50617; BAA09221.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] Z46255; CAA86352.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
SGD	S0001877; GNA1.
GeneCensus	P43577; YFL017C.
InterPro	IPR000182; GCN5acetyltransf. Graphical view of domain structure.
Pfam	PF00583; Acetyltransf; 1.
ProDom	[Domain structure / List of seq. sharing at least 1 domain].
BLOCKS	P43577.
ProtoNet	P43577.
ProtoMap	P43577.
PRESAGE	P43577.
DIP	P43577.
ModBase	P43577.
SWISS-2DPAGE	GET REGION ON 2D PAGE.

Keywords

Transferase; Acyltransferase.

Features

Key	From	To	Length	Description
ACT_SITE	143	143		*POTENTIAL*.
CONFLICT	112	159		GKLLIDQLVTIGFDYGCYKIILDCDEKNVKFYEKCGFSNA GVEMQIRK -> ASS (IN REF. 3).

Featu table viewe

Sequence information

Length: 159 AA Molecular weight: 18135 Da CRC64: 2D2DD2D43A74C6F2 [This is a checksum on the sequence]

```
        10         20         30         40         50         60
         |          |          |          |          |          |
MSLPDGFYIR RMEEGDLEQV TETLKVLTTV GTITPESFSK LIKYWNEATV WNDNEDKKIM

        70         80         90        100        110        120
         |          |          |          |          |          |
QYNPMVIVDK RTETVAATGN IIIERKIIHE LGLCGHIEDI AVNSKYQGQG LGKLLIDQLV

       130        140        150
```

```
          |           |           |
TIGFDYGCYK IILDCDEKNV KFYEKCGFSN AGVEMQIRK
```

P43577 in FASTA format

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Direct BLAST submission at EMBnet-CH/SIB (Switzerland)

Direct BLAST submission at NCBI (Bethesda, USA)

ScanProsite, MotifScan

Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

Feature table viewer (Java)

Search the SWISS-MODEL Repository

NiceProt View of SWISS-PROT: P38628

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[General] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

General information about the entry

Entry name	AGM1_YEAST
Primary accession number	P38628
Secondary accession numbers	None
Entered in SWISS-PROT in	Release 30, October 1994
Sequence was last modified in	Release 31, February 1995
Annotations were last modified in	Release 41, June 2002

Name and origin of the protein

Protein name	Phosphoacetylglucosamine mutase
Synonyms	EC 5.4.2.3 PAGM Acetylglucosamine phosphomutase N-acetylglucosamine-phosphate mutase
Gene name	PCM1 or AGM1 or YEL058W
From	Saccharomyces cerevisiae (Baker's yeast) [TaxID: 4932]
Taxonomy	Eukaryota; Fungi; Ascomycota; Saccharomycotina; Saccharomycetes; Saccharomycetales; Saccharomycetaceae; Saccharomyces.

References

[1] SEQUENCE FROM NUCLEIC ACID.
STRAIN=EBY21-8;
MEDLINE=94164176; PubMed=8119301; [NCBI, ExPASy, EBI, Israel, Japan]
Boles E., Liebetrau W., Hofmann M., Zimmermann F.K.;
"A family of hexosephosphate mutases in Saccharomyces cerevisiae.";
Eur. J. Biochem. 220:83-96(1994).

[2] SEQUENCE FROM NUCLEIC ACID.
STRAIN=S288c / AB972;
Dietrich F.S., Mulligan J.T., Hennessey K.M., Allen E., Araujo R., Aviles E., Berno A., Brennan T., Carpenter J., Chen E., Cherry J.M., Chung E., Duncan M., Guzman E., Hartzell G., Hunicke-Smith S., Hyman R., Kayser A., Komp C., Lashkari D., Lew H., Lin D., Mosedale D., Nakahara K., Namath A., Norgren R., Oefner P., Oh C., Petel F.X., Roberts D., Sehl P., Schramm S., Shogren T., Smith V., Taylor P., Wei Y., Yelton M., Botstein D., Davis R.W.;
Submitted (DEC-1994) to the EMBL/GenBank/DDBJ databases.

EXHIBIT D

[3] CHARACTERIZATION.
STRAIN=EBY21-8;
MEDLINE=94229071; PubMed=8174553; [NCBI, ExPASy, EBI, Israel, Japan]
Hofmann M., Boles E., Zimmermann F.K.;
"Characterization of the essential yeast gene encoding N-acetylglucosamine-phosphate mutase.";
Eur. J. Biochem. 221:741-747(1994).

Comments

- *FUNCTION*: INTERCONVERTS GLCNAC-6-P AND GLCNAC-1-P.
- *CATALYTIC ACTIVITY*: N-acetyl-D-glucosamine 1-phosphate = N-acetyl-D-glucosamine 6-phosphate.
- *PATHWAY*: UDP-GlcNAc biosynthesis from Fru-6-P; third step.
- *SIMILARITY*: BELONGS TO THE PHOSPHOHEXOSE MUTASES FAMILY.

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Cross-references

EMBL	X75816; CAA53452.1; -.[EMBL / GenBank / DDBJ] [CoDingSequence] U18795; AAB65029.1; -.[EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S40263; S40263.
SGD	S0000784; PCM1.
GeneCensus	P38628; YEL058W.
InterPro	IPR001485; PG/PMM_mutase. Graphical view of domain structure.
Pfam	PF00408; PGM_PMM; 1. PF02878; PGM_PMM_I; 1. PF02879; PGM_PMM_II; 1.
PROSITE	PS00710; PGM_PMM; 1.
ProDom	[Domain structure / List of seq. sharing at least 1 domain].
BLOCKS	P38628.
ProtoNet	P38628.
ProtoMap	P38628.
PRESAGE	P38628.
DIP	P38628.
ModBase	P38628.
SWISS-2DPAGE	GET REGION ON 2D PAGE.

Keywords

Isomerase; Phosphorylation.

Features

Key	From	To	Length	Description
ACT_SITE	67	67		FORMS THE PHOSPHOSERINE INTERMEDIATE (*BY SIMILARITY*).
CONFLICT	15	15		T -> M (IN REF. 1).
CONFLICT	196	196		Q -> R (IN REF. 1).
CONFLICT	406	406		E -> G (IN REF. 1).

Feature table viewer

Sequence information

Length: 557 AA Molecular weight: 62066 Da CRC64: 76F17D47D07C920A [This is a checksum on the sequence]

```
         10         20         30         40         50         60
          |          |          |          |          |          |
MKVDYEQLCK LYDDTCRTKN VQFSYGTAGF RTLAKNLDTV MFSTGILAVL RSLKLQGQYV

         70         80         90        100        110        120
          |          |          |          |          |          |
GVMITASHNP YQDNGVKIVE PDGSMLLATW EPYAMQLANA ASFATNFEEF RVELAKLIEH

        130        140        150        160        170        180
          |          |          |          |          |          |
EKIDLNTTVV PHIVVGRDSR ESSPYLLRCL TSSMASVFHA QVLDLGCVTT PQLHYITDLS

        190        200        210        220        230        240
          |          |          |          |          |          |
NRRKLEGDTA PVATEQDYYS FFIGAFNELF ATYQLEKRLS VPKLFIDTAN GIGGPQLKKL

        250        260        270        280        290        300
          |          |          |          |          |          |
LASEDWDVPA EQVEVINDRS DVPELLNFEC GADYVKTNQR LPKGLSPSSF DSLYCSFDGD

        310        320        330        340        350        360
          |          |          |          |          |          |
ADRVVFYYVD SGSKFHLLDG DKISTLFAKF LSKQLELAHL EHSLKIGVVQ TAYANGSSTA

        370        380        390        400        410        420
          |          |          |          |          |          |
YIKNTLHCPV SCTKTGVKHL HHEAATQYDI GIYFEANGHG TIIFSEKFHR TIKSELSKSK

        430        440        450        460        470        480
          |          |          |          |          |          |
LNGDTLALRT LKCFSELINQ TVGDAISDML AVLATLAILK MSPMDWDEEY TDLPNKLVKC

        490        500        510        520        530        540
          |          |          |          |          |          |
IVPDRSIFQT TDQERKLLNP VGLQDKIDLV VAKYPMGRSF VRASGTEDAV RVYAECKDSS

        550
          |
KLGQFCDEVV EHVKASA
```

P38628 in FASTA format

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Direct BLAST submission at EMBnet-CH/SIB (Switzerland)

Direct BLAST submission at NCBI (Bethesda, USA)

ScanProsite, MotifScan

Tools Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

 Feature table viewer (Java)

 Search the SWISS-MODEL Repository

NiceProt View of SWISS-PROT: P43123

Printer-friendly view | Quick BlastP search

[General] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

General information about the entry

Entry name	UAP1_YEAST
Primary accession number	P43123
Secondary accession numbers	None
Entered in SWISS-PROT in	Release 32, November 1995
Sequence was last modified in	Release 32, November 1995
Annotations were last modified in	Release 41, June 2002

Name and origin of the protein

Protein name	UDP-N-acetylglucosamine pyrophosphorylase
Synonym	EC 2.7.7.23
Gene name	UAP1 or QRI1 or YDL103C or D2362
From	Saccharomyces cerevisiae (Baker's yeast) [TaxID: 4932]
Taxonomy	Eukaryota; Fungi; Ascomycota; Saccharomycotina; Saccharomycetes; Saccharomycetales; Saccharomycetaceae; Saccharomyces.

References

[1] SEQUENCE FROM NUCLEIC ACID, AND CHARACTERIZATION.
STRAIN=A451;
MEDLINE=98269105; PubMed=9603950; [NCBI, ExPASy, EBI, Israel, Japan]
Mio T., Yabe T., Arisawa M., Yamada-Okabe H.;
"The eukaryotic UDP-N-acetylglucosamine pyrophosphorylases: gene cloning, protein expression, and catalytic mechanism.";
J. Biol. Chem. 273:14392-14397(1998).

[2] SEQUENCE FROM NUCLEIC ACID.
MEDLINE=95242841; PubMed=7725801; [NCBI, ExPASy, EBI, Israel, Japan]
Simon M., Benit P., Vassal A., Dubois C., Faye G.;
"Sequence of the PHO2-POL3 (CDC2) region of chromosome IV of Saccharomyces cerevisiae.";
Yeast 10:1653-1656(1994).

[3]
SEQUENCE FROM NUCLEIC ACID.
STRAIN=S288c / FY1679;
MEDLINE=97051597; PubMed=8896274; [NCBI, ExPASy, EBI, Israel, Japan]
Saiz J.E., Buitrago M.J., Garcia R., Revuelta J.L., del Rey F.;
"The sequence of a 20.3 kb DNA fragment from the left arm of Saccharomyces cerevisiae

EXHIBIT E

chromosome IV contains the KIN28, MSS2, PHO2, POL3 and DUN1 genes, and six new open reading frames.";
Yeast 12:1077-1084(1996).

Comments

- *CATALYTIC ACTIVITY*: UTP + N-acetyl-alpha-D-glucosamine 1-phosphate = diphosphate + UDP-N-acetyl-D-glucosamine.
- *PATHWAY*: UDP-GlcNAc biosynthesis from Fru-6-P; fourth (last) step.
- *SUBCELLULAR LOCATION*: Cytoplasmic *(By similarity)*.

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Cross-references

EMBL	AB011272; BAA31203.1; -.[EMBL / GenBank / DDBJ] [CoDingSequence] X79380; CAA55927.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] X95644; CAA64910.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] Z74151; CAA98670.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
SGD	S0002261; QRI1.
GeneCensus	P43123; YDL103C.
InterPro	IPR002618; UDPGP. Graphical view of domain structure.
Pfam	PF01704; UDPGP; 1.
ProDom	[Domain structure / List of seq. sharing at least 1 domain].
BLOCKS	P43123.
ProtoNet	P43123.
ProtoMap	P43123.
PRESAGE	P43123.
DIP	P43123.
ModBase	P43123.
SWISS-2DPAGE	GET REGION ON 2D PAGE.

Keywords

Transferase; Nucleotidyltransferase.

Features

Key	From	To	Length	Description
SITE	112	112	1	BINDING SITE FOR GLCNAC-1-P *(PROBABLE)*.
ACT_SITE	116	116		*POTENTIAL*.
ACT_SITE	123	123		*POTENTIAL*.
MUTAGEN	111	111		G->A: DECREASE OF ACTIVITY.
MUTAGEN	112	112		G->A: LOSS OF ACTIVITY.
MUTAGEN	114	114		G->A: DECREASE OF ACTIVITY.
MUTAGEN	115	115		T->A: DECREASE OF ACTIVITY.
MUTAGEN	116	116		R->A: LOSS OF ACTIVITY.
MUTAGEN	117	117		L->A: DECREASE OF ACTIVITY.
MUTAGEN	122	122		P->A: DECREASE OF ACTIVITY.
MUTAGEN	123	123		K->A: LOSS OF ACTIVITY.

Feature table viewer

Sequence information

Length: 477 AA Molecular weight: 53476 Da CRC64: 2D656E31C17805FD [This is a checksum on the sequence]

```
          10         20         30         40         50         60
           |          |          |          |          |          |
MTDTKQLFIE AGQSQLFHNW ESLSRKDQEE LLSNLEQISS KRSPAKLLED CQNAIKFSLA

          70         80         90        100        110        120
           |          |          |          |          |          |
NSSKDTGVEI SPLPPTSYES LIGNSKKENE YWRLGLEAIG KGEVAVILMA GGQGTRLGSS

         130        140        150        160        170        180
           |          |          |          |          |          |
QPKGCYDIGL PSKKSLFQIQ AEKLIRLQDM VKDKKVEIPW YIMTSGPTRA ATEAYFQEHN

         190        200        210        220        230        240
           |          |          |          |          |          |
YFGLNKEQIT FFNQGTLPAF DLTGKHFLMK DPVNLSQSPD GNGGLYRAIK ENKLNEDFDR

         250        260        270        280        290        300
           |          |          |          |          |          |
RGIKHVYMYC VDNVLSKIAD PVFIGFAIKH GFELATKAVR KRDAHESVGL IATKNEKPCV

         310        320        330        340        350        360
           |          |          |          |          |          |
IEYSEISNEL AEAKDKDGLL KLRAGNIVNH YYLVDLLKRD LDQWCENMPY HIAKKKIPAY

         370        380        390        400        410        420
           |          |          |          |          |          |
DSVTGKYTKP TEPNGIKLEQ FIFDVFDTVP LNKFGCLEVD RCKEFSPLKN GPGSKNDNPE

         430        440        450        460        470
           |          |          |          |          |
TSRLAYLKLG TSWLEDAGAI VKDGVLVEVS SKLSYAGENL SQFKGKVFDR SGIVLEK
```

P43123 in FASTA format

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Direct BLAST submission at EMBnet-CH/SIB (Switzerland)

Direct BLAST submission at NCBI (Bethesda, USA)

ScanProsite, MotifScan

Tools Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

Feature table viewer (Java)

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